amendment to claim 17, claim 18 now further limits the subject matter of the previous claim, thereby obviating the basis of this rejection.

Rejection of the claims under 35 U.S.C. § 112, ¶ 1

The specification is objected to, and claims 2-4 stand rejected, under section 112, first paragraph, for allegedly failing to teach adequately how to make and/or use the invention. The Examiner asserts that the specification does not provide enablement for a device comprising osteogenic protein wherein said protein is an amino acid sequence variant of the recited osteogenic proteins or wherein the osteogenic protein comprises an amino acid sequence having at least 70% sequence homology with the C-terminal 102-106 amino acids, including the conserved seven cysteine domain, of human OP-1 without regard to the functional activity of the osteogenic protein. Applicants respectfully traverse the rejection to the extent that it is maintained over the claims as amended and the arguments set forth herein.

Applicants respectfully submit that the class of proteins embraced by claims 2-4 is sufficiently circumscribed by the instant specification. "Osteogenic proteins" as contemplated by the instant application are defined structurally, biochemically and functionally on at least pages 26-28. Contrary to assertions stated in the Office Action, Applicants' claimed invention does not embrace an unduly broad spectrum of osteogenic protein variants, nor does identification of osteogenic proteins encompassed by the claims necessitate undue experimentation by the skilled artisan. As expressly stated in Applicants' specification (see, for example, at least pages 2 and 22-23), Applicants' invention contemplates a specific class of proteins which can induce the full cascade of morphogenic events culminating in the formation of new endochondral bone. These events include a) inducing recruitment of accessible progenitor cells and stimulating their proliferation, b) thereby inducing differentiation into chondrocytes and osteoblasts, and c) further inducing differentiation of intermediate cartilage, vascularization, bone formation, remodeling and marrow differentiation. (See page 2, lines 17-23.) Towards this end, Applicants provide

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specific guidance in the instant specification by describing an assay for measuring all the critical events associated with endochondral bone morphogenesis (see page 56, line 1 through page 57, line 24, as well as the references cited and incorporated by reference thereon).

Keeping this definition of "osteogenic protein" in mind, Applicants submit that the specification does provide adequate guidance for one of ordinary skill in the art to make and/or use the invention of claims 2 and 3, as amended. Claims 2 and 3 have been amended to include only "conservative" amino acid sequence variants of the specifically recited osteogenic proteins. Conservative changes in the amino acid sequence of osteogenic proteins is defined in the specification on page 27, line 8 through page 28, line 3. Conservative substitutions for corresponding residues in a reference sequence are defined thereon as "those that are physically or functionally similar to the corresponding reference residues." (See page 27, line 15.) Furthermore, conservative substitutions are also defined thereon to include "those wherein one or more amino acid residues differs from the corresponding residue of a reference sequence . . . provided that this difference does not destroy bone morphogenic activity." (See page 27, lines 9-12.) Finally, conservative substitutions are also defined by Dayhoff, *et al.* (1978), 5 Atlas of Protein Sequence and Structure, Suppl. 3, ch. 22 (pp. 354-352), Natl. Biomed. Res. Found., Washington, D.C. 20007, the teachings of which are incorporated by reference thereon. Conservative amino acid sequence variants are therefore adequately enabled by the specification as the definition of "conservative" is adequately defined in the specification and is also defined with respect to the functional activity of the proteins.

Applicants further submit that the specification also provides adequate guidance for one of ordinary skill in the art to make and/or use the invention of claim 4. Claim 4 has been amended only to correct typographical errors not pertinent to this rejection. On page 29, line 24 through page 30, line 24, of the specification, Applicants provide guidance in determining an osteogenic protein having 70% homology with the C-terminal 102-106 amino acids, including

the conserved seven cysteine domain of human OP-1. Thereon Applicants describe how percent levels of homology may be determined by aligning a candidate osteogenic protein with the sequence of a reference protein using the alignment method of Needleman, *et al.* (1970), J. Mol. Biol. 48:443-453. (See page 30, lines 3-5.) The functional activity of these amino acid sequences is also part of their definition, as described above.

Section 112, first paragraph, requires that Applicants teach how to make, use and test the claimed invention in sufficient detail to permit the skilled artisan to practice the claimed subject matter with a reasonable expectation of success. Applicants respectfully submit that the instant specification complies with this legal standard. The rejection of claims 2-4 under section 112, first paragraph, should be withdrawn.

Rejection of the claims under 35 U.S.C. § 112, ¶ 2

Claims 26-30 and 34 stand rejected under 35 U.S.C. § 112, ¶ 2 as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Claim 34 has been canceled, thereby obviating the basis for its rejection. Applicants respectfully traverse the other rejections to the extent they are maintained over the claim amendments and arguments presented herein.

The Examiner asserts that claims 26-28 are indefinite over the recitation of "defect site." Applicants submit that the phrase "defect site" is definite in view of the definition of "defect site" recited in the specification at page 16, line 1 through page 17, line 2. As stated thereon, a "defect site" can include "a bony structural disruption requiring repair." The Examiner also asserts that claims 26-30 are indefinite because the claims lack a process step that clearly relates back to the preamble and do not make clear the intended effect to be achieved. Applicants again note the definition of "defect site" on page 16, line 1 through page 17, line 2 of the specification. The recitation of "defect site" in claim 26, as amended, relates the process step of providing an

osteogenic device back to the preamble of "for inducing local bone or cartilage formation at a defect site." Furthermore, claim 26 has been amended to recite the intended effect to be achieved. Applicants submit that claim 26, as amended, is definite. Claims 27-30 are also definite as depending from the definite base claim.

Rejection of the claims under 35 U.S.C. § 102(b)

Claims 1-4, 7-15 and 20-24 currently stand rejected as being anticipated under 35 U.S.C. § 102(b). Claims 1, 7-15, 20-22 and 24 are rejected as anticipated by Amman, *et al.*, U.S. Patent No. 5,422,340 (hereinafter "Amman"). Claims 1-4 and 7-15 are rejected as anticipated by O'Leary, *et al.*, U.S. Patent No. 5,073,373 (hereinafter "O'Leary"). Finally, claims 23 and 24 are rejected as anticipated by Lindstrom, *et al.*, U.S. Patent No. 5,366,964 (hereinafter "Lindstrom"). Applicants respectfully traverse these rejections to the extent they are maintained over the claim amendments and arguments presented herein.

In order for a prior art reference to anticipate under 35 U.S.C. § 102, all elements of the claim must be found in a single piece of prior art. In re Bond, 910 F.2d 831, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). Applicants respectfully submit that none of the cited reference identically discloses all elements of the claims, as amended.

Rejection over Amman

The Examiner rejected claims 1, 7-15, 20-22 and 24 under 35 U.S.C. § 102(b) as being anticipated by Amman, because Amman discloses a composition comprising an osteogenic protein, wherein the osteogenic protein is TGF-β. As explained below, TGF-β does not fall within Applicants' defined genus of osteogenic proteins. As expressly stated in Applicants' specification (see, for example, at least pages 2 and 22-23), Applicants' invention contemplates a specific class of proteins which can induce the full cascade of morphogenic events culminating in the formation of new endochondral bone. These events include a) inducing recruitment of

accessible progenitor cells and stimulating their proliferation, b) thereby inducing differentiation into chondrocytes and osteoblasts, and c) further inducing differentiation of intermediate cartilage, vascularization, bone formation, remodeling and marrow differentiation. (See page 12, definition of "endochondral bone formation.")

The protein TGF-β does not fall within this definition of osteogenic protein. See, for example, Beck, *et al.*, (1991), J. Bone and Min. Res. 6:1257-1265 at p. 1264, a copy of which is enclosed for the Examiner's convenience. The authors of the Beck article note that TGF-β results in bone formation without cartilaginous intermediates, *i.e.,* non-endochondral bone, whereas bone morphogenic proteins (hereinafter "BMPs") or "osteogenic proteins" induce bone formation with a cartilaginous intermediate, *i.e.,* non-endochondral bone. Finally, Applicants make clear that TGF-β is not included as an osteogenic protein on page 22, lines 3-7, on which they state that "[I]n addition to osteogenic proteins, various growth factors . . . can also be contained within an improved osteogenic device. Thus, various known growth factors such as . . . TGF-β can be combined with an improved osteogenic device and delivered to a defect site."

Applicants submit, therefor that Amman does not teach the use of an osteogenic protein, as contemplated by the invention, in conjunction with a matrix and binding agent as recited in claims 1 and 20. Since Amman does not teach the element of an osteogenic protein, as contemplated by the invention, it does not contain all of the elements of claims 1 and 20, and it therefore does not anticipate claims 1 and 20 under 35 U.S.C. § 102(b). Applicants submit therefore that claims 1 and 20 are allowable under 35 U.S.C. § 102(b) over Amman, and that claims 7-15, 21, 22 and 24 are also allowable as depending from allowable base claims.

[redacted]

Rejection over O'Leary

The Examiner rejected claims 1-4 and 7-15 under 35 U.S.C. § 102(b) as being anticipated by O'Leary, because O'Leary discloses a composition for use in bone repair comprising demineralized bone powder, BMPs, one or more binding agents, and a wetting agent. Claims 1 and 7 have been amended to further distinguish the invention over O'Leary. Specifically, claims 1 and 7 have been amended to make clear that the matrix of the invention does not include demineralized bone powder. Since O'Leary only teaches the use of demineralized bone powder as a matrix, and since the instant invention does not contemplate the use of demineralized bone powder as a matrix, all of the elements of claim 1, as amended, are not taught by O'Leary. Since O'Leary does not teach the element of a matrix that is not demineralized bone powder, it does not contain all of the elements of claim 1, as amended, and it therefore does not anticipate claim 1 under 35 U.S.C. § 102(b). Applicants submit therefore that claim 1 is allowable under 35 U.S.C. § 102(b) over O'Leary, and that claims 2-4 and 7-15 are also allowable as depending from a now allowable base claim.

Rejection over Lindstrom

The Examiner rejected claims 23 and 24 under 35 U.S.C. § 102(b) as being anticipated by Lindstrom, because Lindstrom discloses a composition comprising an osteogenic protein, wherein the osteogenic protein is TGF-β. As noted above in connection with the rejection over Amman, osteogenic protein, as defined by the specification, does not include TGF-β. As such, the element of an osteogenic protein, as contemplated by the invention, is not included in the Lindstrom reference. Applicants submit therefore that claims 23 and 24 are allowable under 35 U.S.C. § 102(b) over Lindstrom.

[redacted]

Rejection of the claims under 35 U.S.C. § 103(a)

Claims were also rejected as being unpatentable under 35 U.S.C. § 103(a). Claims 1 and 6 are rejected as being unpatentable over O'Leary in view of Ogawa, *et al.*, (1992) J. Biol. Chem. 267:14233-7 (hereinafter "Ogawa"). Claims 1 and 9 are rejected as being unpatentable over Amman in view of LeGeros, *et al.*, II CRC Handbook of Bioactive Ceramics (CRC Press), pp. 17-28 (1990) (hereinafter "LeGeros"). Claims 1, 20-22, 32 and 33 are rejected as being unpatentable over Amman. Claims 23, 24, and 26-30 are rejected as being unpatentable over Lindstrom. Claims 1, 5, 17-19 and 26-31 are rejected as being unpatentable over Cook, *et al.*, (1994) J. Bone and Joint Surg., 76-A(6):827-38 (hereinafter "Cook") in view of O'Leary. Finally, claims 1, 15-19 and 25 are rejected as unpatentable over Cook, in view of O'Leary and further in view of Kuberasampath, *et al.*, U.S. Patent No. 5,171,574 (hereinafter "Kuberasampath"). These rejections are traversed to the extent they are maintained over the claims as amended and the arguments presented herein.

Rejection of claims 1 and 6

The Examiner rejects claims 1 and 6 as being unpatentable under 35 U.S.C. § 103(a) over O'Leary in view of Ogawa, because Ogawa teaches that TGF-β and BMP synergize in promoting formation of endochondral bone and O'Leary teaches a composition for bone repair comprising a BMP. The Examiner asserts that it would have been obvious to one of ordinary skill in the art to combine the composition of O'Leary with the teachings of Ogawa to make composition a comprising two osteogenic proteins, such as TGF-β and a BMP.

Applicants respectfully submit that the combination of elements comprising the invention defined by Applicants' claims, as now pending, is neither taught nor suggested by either of the cited references taken singly or combined. Claim 1, as amended, defines a device for inducing local bone or cartilage formation comprising osteogenic protein, matrix derived from non-

[redacted]

synthetic, non-polymeric material that is not demineralized bone, and binding agent. Claim 6 defines this device with at least two different osteogenic proteins. O'Leary teaches the use of demineralized bone as a matrix, but it does not teach or suggest the use of any other matrix materials. Ogawa teaches the use of TGF-β in combination with a BMP, but, as discussed above, TGF-β is not an osteogenic protein as defined by the invention. Ogawa does not teach the use of two different osteogenic proteins as that term is defined by the present invention. Since neither reference taken singly or combined recites all of the elements of claim 1, as amended, or the elements of claim 6, they cannot support a rejection of these claims under 35 U.S.C. § 103(a).

Rejection of claims 1 and 9

The Examiner rejects claims 1 and 9 as being unpatentable under 35 U.S.C. § 103(a) over Amman in view of LeGeros, because LeGeros teaches the use of a combination of hydroxyapatite (HA) and tricalcium phosphate (TCP) as a matrix and Amman teaches a composition comprising TGF-β, matrix and binder. The Examiner asserts that it would have been obvious to one of ordinary skill in the art to combine the composition of Amman with the teachings of LeGeros to make a composition comprising HA, TCP and an osteogenic protein.

Applicants respectfully submit that the combination of elements comprising the invention defined by Applicants' claims, as now pending, is neither taught nor suggested by either of the cited references taken singly or combined. Claim 1, as amended, defines a device for inducing local bone or cartilage formation comprising osteogenic protein, matrix derived from non-synthetic, non-polymeric material that is not demineralized bone, and binding agent. Claim 9 defines this device with at least two different matrices. Amman teaches the use of TGF-β, but, as discussed above, TGF-β is not an osteogenic protein as defined by the invention. Amman does not teach the use of an osteogenic protein as that term is defined by the present invention. LeGeros also does not teach or suggest the use of an osteogenic protein as that term is defined by the invention. Since neither reference taken singly or combined recites all of the elements of

claim 1, as amended, or the elements of claim 9, they cannot support a rejection of these claims under 35 U.S.C. § 103(a).

Rejection of claims 1, 20-22, 32 and 33

The Examiner rejects claims 1, 20-22, 32 and 33 as being unpatentable under 35 U.S.C. § 103(a) over Amman, because Amman teaches a composition comprising TGF-β, matrix and binder. The Examiner asserts that it would have been obvious to one of ordinary skill in the art to combine the composition of Amman in a kit.

Again, Applicants respectfully submit that Amman does not teach or suggest the use of an osteogenic protein as that term is defined by the invention. Since the element of an osteogenic protein as defined by the invention is not present in Amman, it cannot support a rejection of claims 1, 20-22, 32 and 33 under 35 U.S.C. § 103(a).

Rejection of claims 23, 24 and 26-30

The Examiner rejects claims 23, 24 and 26-30 as being unpatentable under 35 U.S.C. § 103(a) over Lindstrom, because Lindstrom teaches a composition comprising TGF-β, 0.01%-10% binding agent, and 0.1 ng/ml-1 g/ml matrix for use in orthopedic applications. The Examiner asserts that it would have been obvious to one of ordinary skill in the art to use the composition of Lindstrom to heal bone.

Applicants respectfully submit that Lindstrom does not teach or suggest all of the elements of the claims. Lindstrom only teaches the use of TGF-β. Lindstrom therefore does not teach or suggest the use of an osteogenic protein as that term is defined by the invention, as is described above. Since the element of an osteogenic protein as defined by the invention is not present in Lindstrom, it cannot support a rejection of claims 23, 24 and 26-30 under 35 U.S.C. § 103(a).

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Rejection of claims 1, 5, 17-19 and 26-31

The Examiner rejects claims 1, 5, 17-19 and 26-31 as being unpatentable under 35 U.S.C. § 103(a) over Cook in view of O'Leary. The Examiner asserts that Cook teaches a composition comprising OP-1 and collagen derived from demineralized bone for use in the induction of bone formation, that the composition comprises the equivalent of 1000mg collagen to 1.25-5.0 mg of OP-1, and that an experimental bone defect could be filled completely with the composition. The Examiner then asserts that O'Leary teaches a composition comprising demineralized bone powder, which comprises collagen as taught by Cook, BMPs, and carboxymethylcellulose (hereinafter "CMC"). The Examiner asserts that it would have been obvious to one of ordinary skill in the art to combine the composition of Cook with the teachings of O'Leary to obtain the device of the present invention.

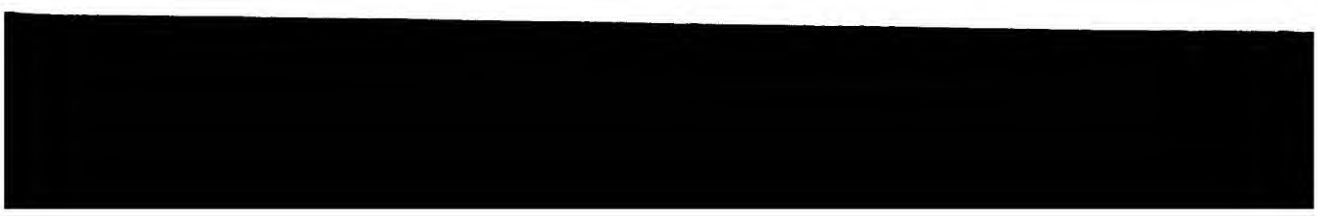
Applicants respectfully submit that the above-cited references cannot be combined to support a rejection under 35 U.S.C. § 103(a), because O'Leary does not teach or suggest the use of collagen without demineralized bone. Cook teaches a combination of collagen and OP-1 for bone formation, but it does teach or suggest the use of a binder, such as CMC. O'Leary teaches the use of demineralized bone, collagen lattice, BMP and CMC, but it does not teach or suggest that a composition that does not contain demineralized bone can support the formation of bone. While collagen may be one of the many components of demineralized bone, the two are not identical. O'Leary acknowledges this at column 3, lines 1 and 2, where he states that collagen lattices may be added to the demineralized bone matrix. Likewise, in claim 4 of O'Leary, he teaches the use of collagen lattice only in conjunction with demineralized bone powder. O'Leary, therefore, does not teach or suggest the use of collagen matrix without demineralized bone powder. O'Leary, therefore, teaches away from the use of any matrix material other than demineralized bone powder. A reference teaches away from the claimed invention when a person of ordinary skill in the art, upon reading the reference, would be lead in a direction other

than that taken by the applicant. In re Gurley, 27 F.3d 551, 31 U.S.P.Q. 2d 1130 (Fed. Cir. 1994). Since one of ordinary skill in the art reading O'Leary would not be motivated to make a composition containing collagen and BMP without also including demineralized bone powder, O'Leary cannot be combined with Cook, or any other reference, to support a rejection of claims 1, 5, 17-19 and 26-31 under 35 U.S.C. § 103(a).

Rejection of claims 1, 15-19 and 25

The Examiner rejects claims 1, 5, 17-19 and 26-31 as being unpatentable under 35 U.S.C. § 103(a) over Cook in view of O'Leary, as described above, and further in view of Kuberasampath. The Examiner asserts that it would have been obvious to one of skill in the art to combine Cook and O'Leary, as described above, to obtain the device of claims 1, 15-19 and 25 by adding saline, as taught by Kuberasampath.

Again, Applicants respectfully submit that one of ordinary skill in the art would not have been motivated to combine the teachings of O'Leary with any other reference to obtain the claimed invention, because, as described above, O'Leary teaches away from the claimed invention. O'Leary does not teach that collagen may be used in a composition for bone growth without demineralized bone powder. Since one of ordinary skill in the art reading O'Leary would not be motivated to make a composition containing collagen and BMP without also including demineralized bone powder, O'Leary cannot be combined with Cook or Kuberasampath to support a rejection of claims 1, 5, 17-19 and 26-31 under 35 U.S.C. § 103(a).



CONCLUSION

In view of the arguments set forth above and the claim amendments presented herein, Applicants respectfully submit that the pending claims as amended are in condition for immediate allowance. Reconsideration respectfully is requested. The Examiner is urged to contact the undersigned to discuss the amendment and/or remarks presented herein.

Respectfully submitted,

Dated: May 11, 1998

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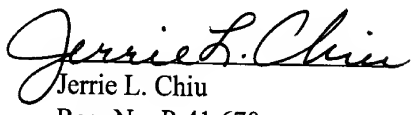

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